

Figure 1

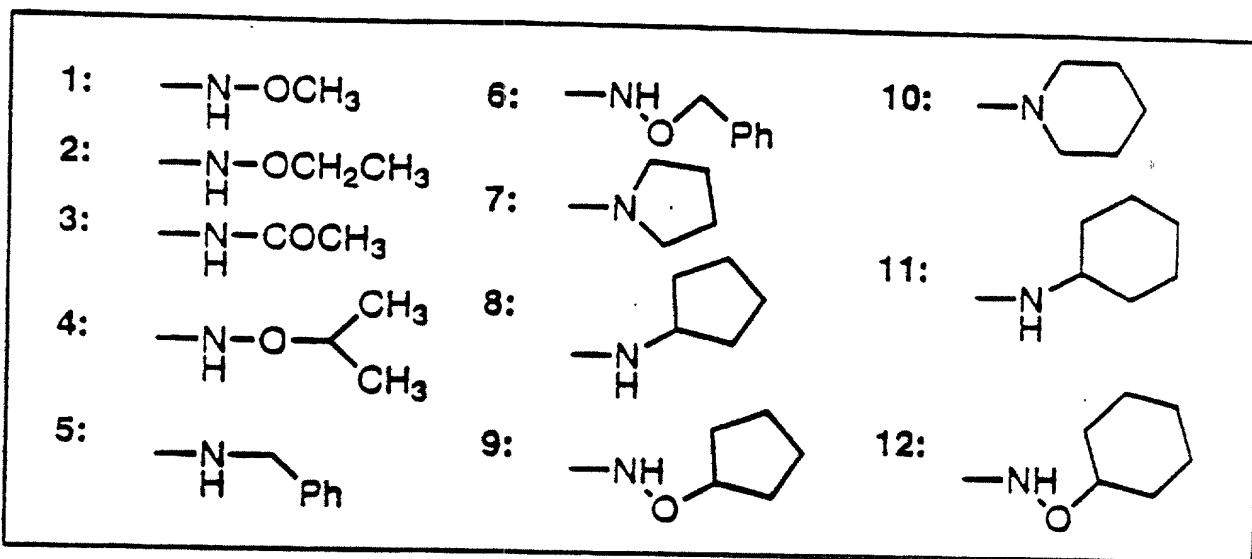
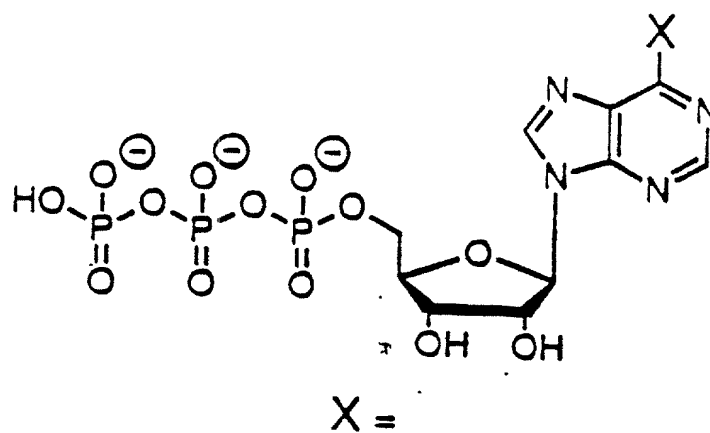


Figure 2

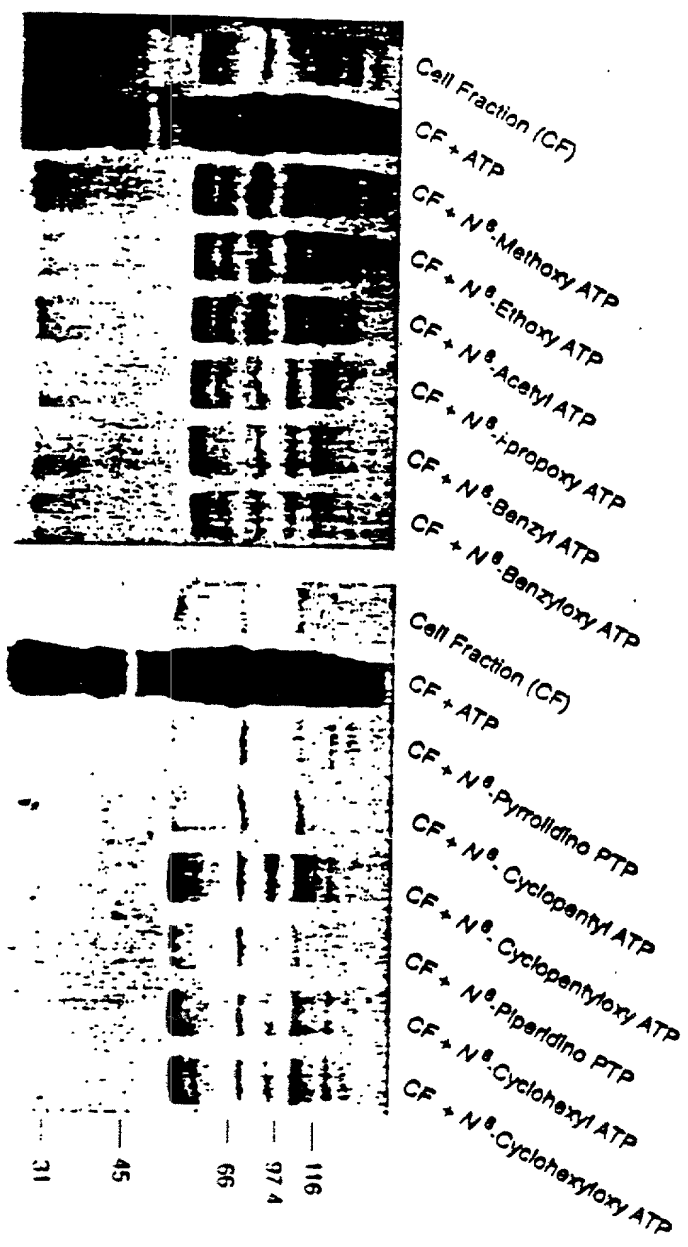


Figure 3

10044967-041502

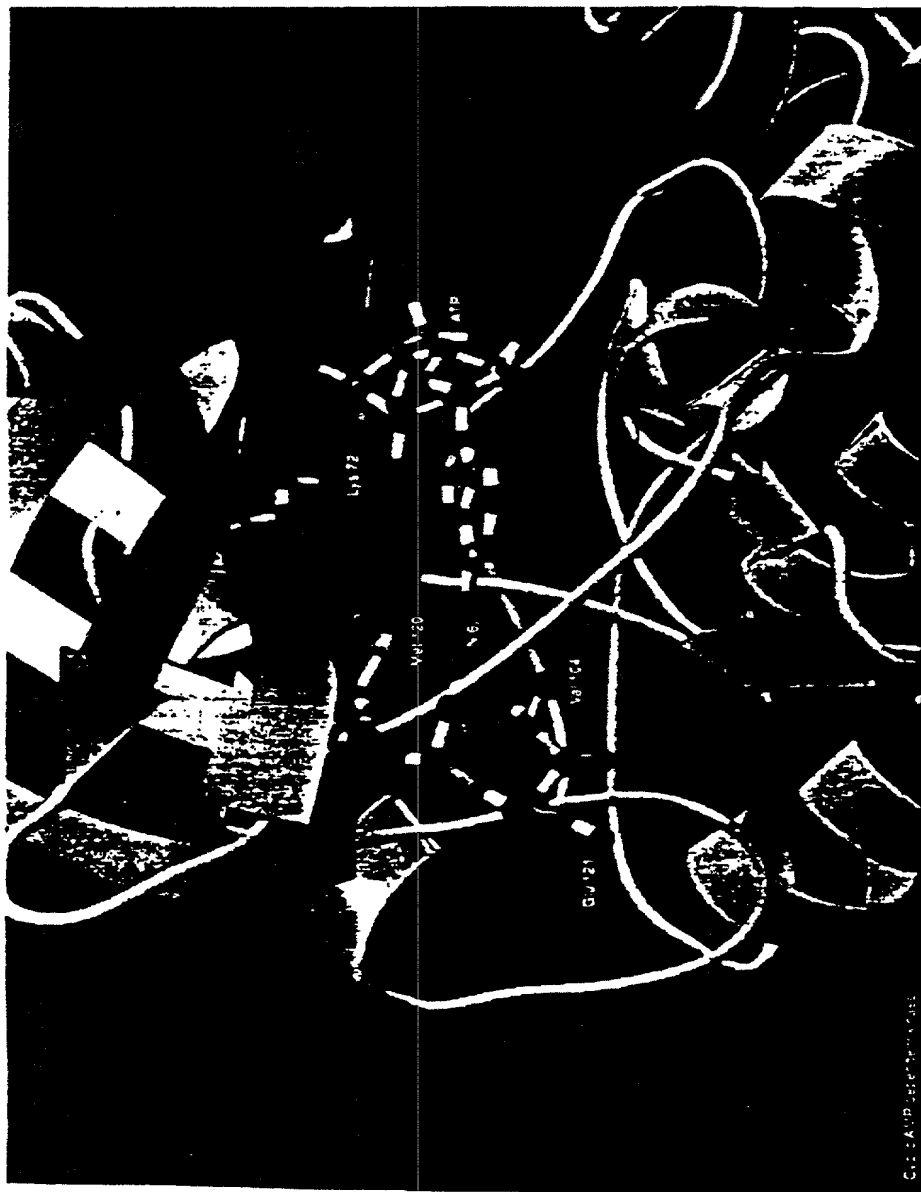


Figure 4

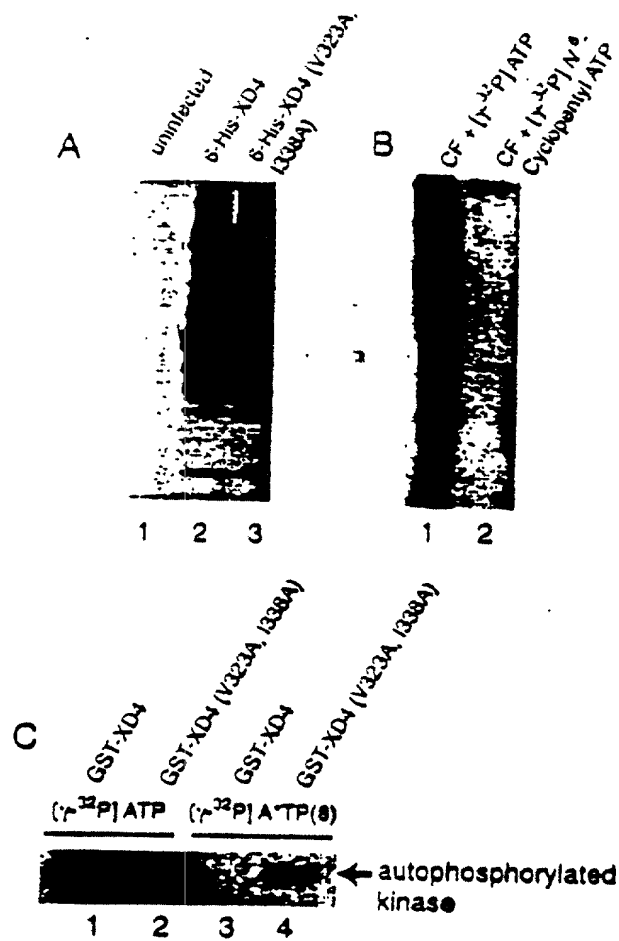


Figure 5

■ GST-XD4
 ▨ GST-XD4(V323A,I338A)

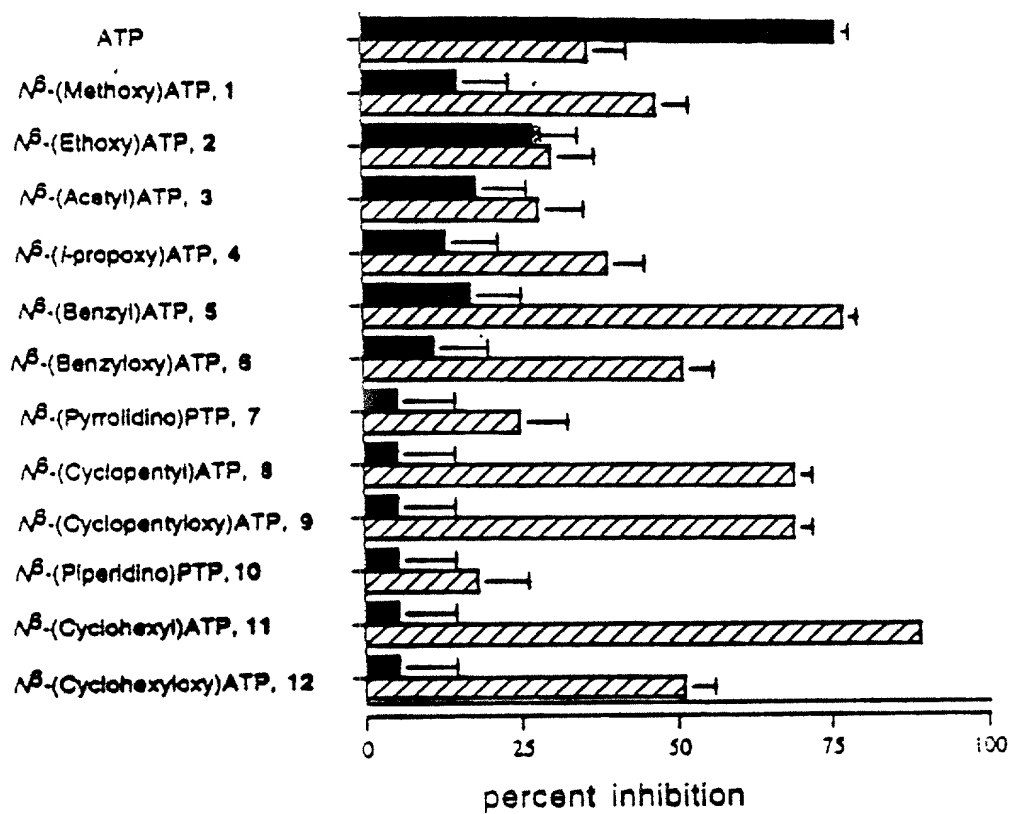


Figure 6

1024967-04100

$[\gamma\text{-}^{32}\text{P}] \text{ATP}$



I338A I338S

$[\gamma\text{-}^{32}\text{P}] \text{N}^6\text{-cyclopentyl ATP}$



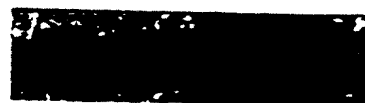
I338A I338S

$[\gamma\text{-}^{32}\text{P}] \text{ATP}$



I338A I338G

$[\gamma\text{-}^{32}\text{P}] \text{N}^6\text{-cyclopentyl ATP}$



I338A I338G

Figure 7

4004967-04500

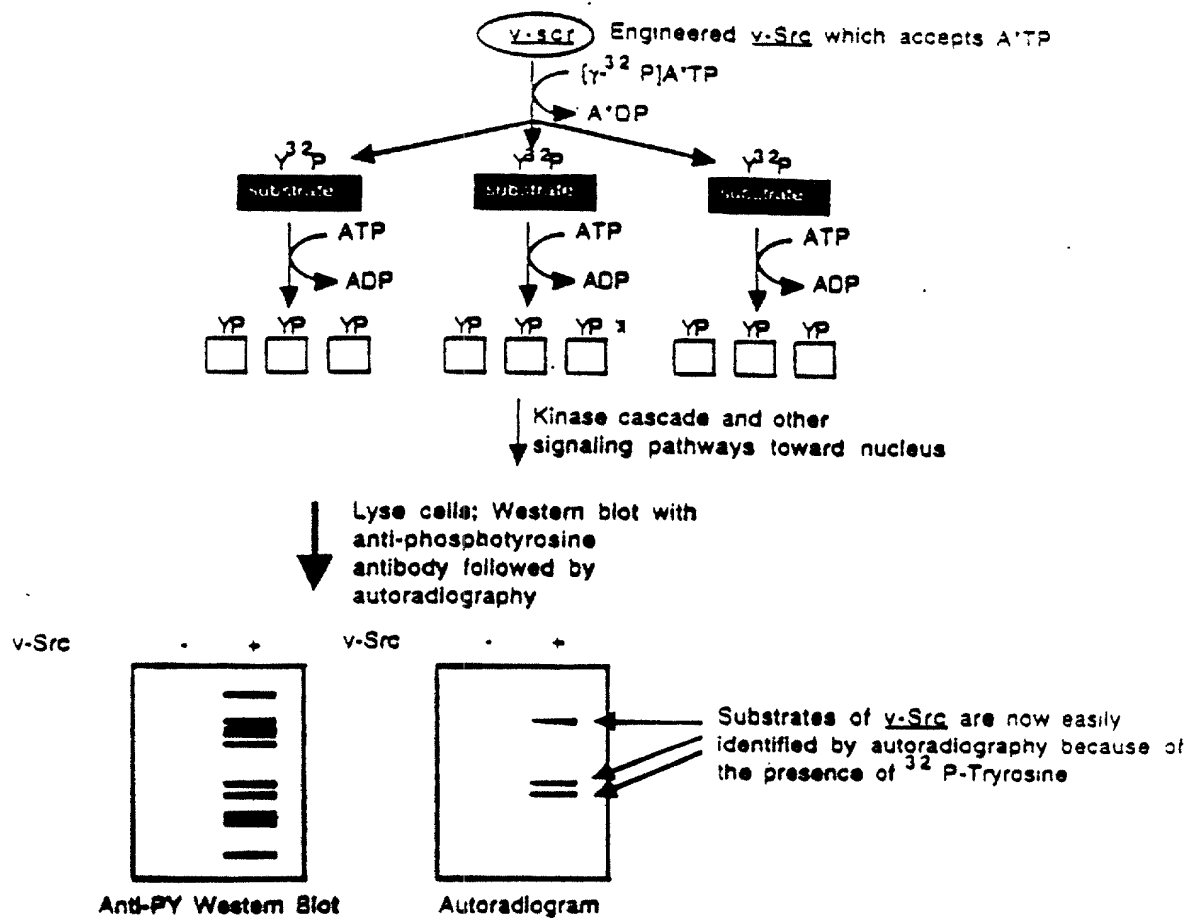
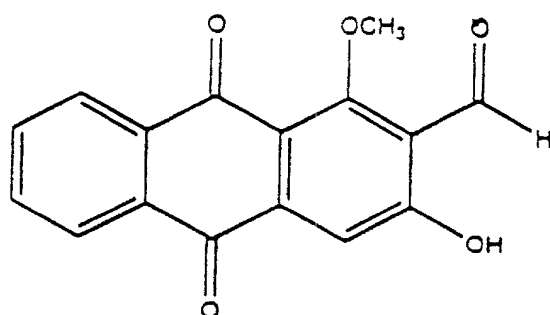


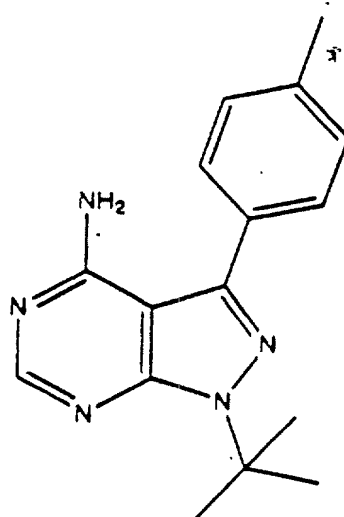
Figure 8

A. Damniacanthal



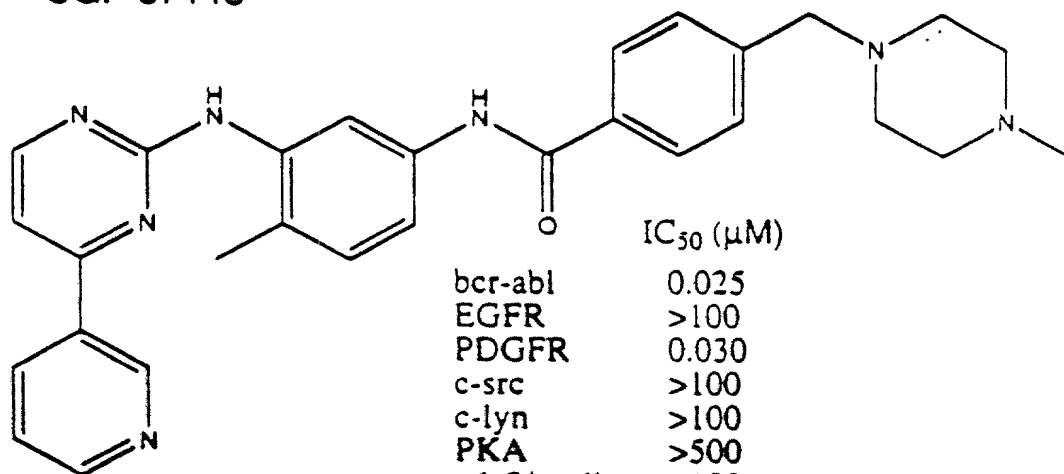
	IC ₅₀ (μM)
lck	0.10
fyn	2.09
src	0.68
erbB2	3.5

B. PP1



	IC ₅₀ (μM)
lck	0.005
fyn	0.006
src	0.17
hck	0.020
zap-70	>100
JAK2	>50
EGFR	0.25

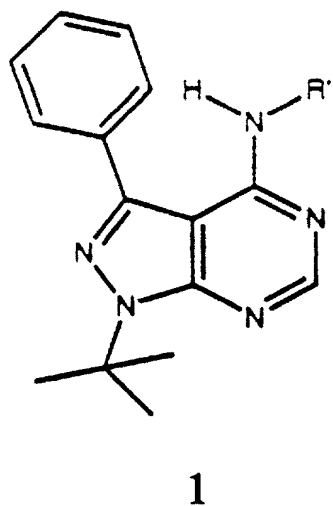
C. CGP 57148



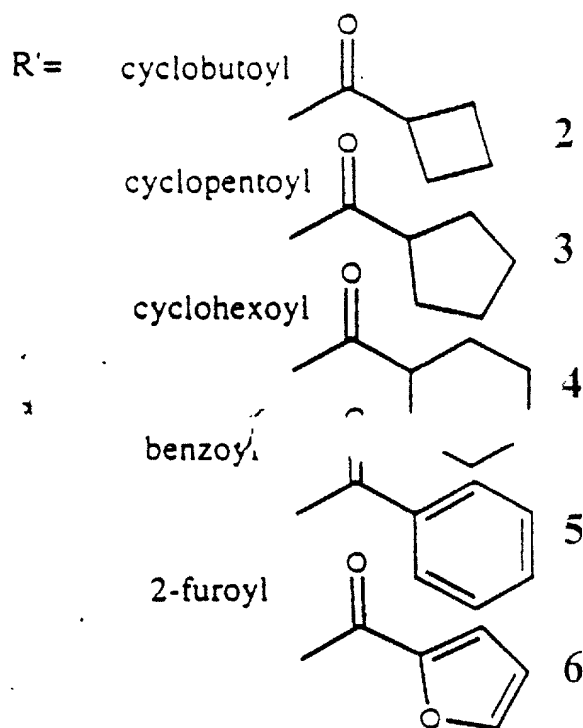
	IC ₅₀ (μM)
bcr-abl	0.025
EGFR	>100
PDGFR	0.030
c-src	>100
c-lyn	>100
PKA	>500
cdc2/cyclin	>100

Figure 9

A. N-4 Acyl Analogues



B.



C. *In vitro* Inhibition Data

R' =	IC ₅₀ (μM)		
	WT fyn	WT src	I338G src
H	0.08	35	<1
cyclobutoyl		>>400	12
cyclopentoyl	400	>>400	5
cyclohexoyl	50	>>400	20
benzoyl	>400	>>400	50
2-furoyl		>>400	150

Figure 10

A

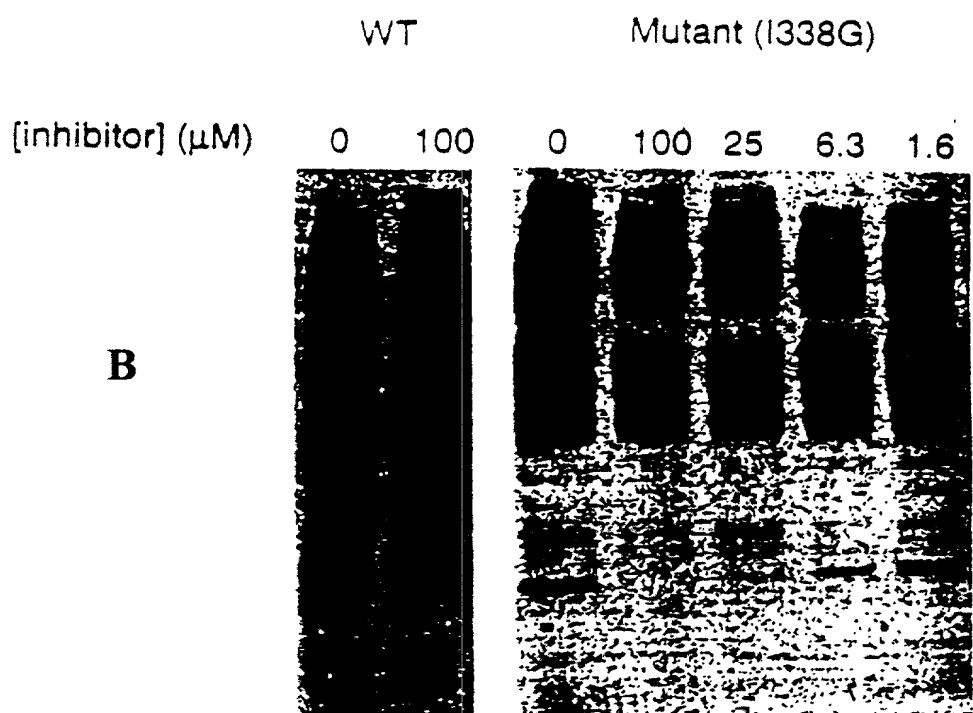
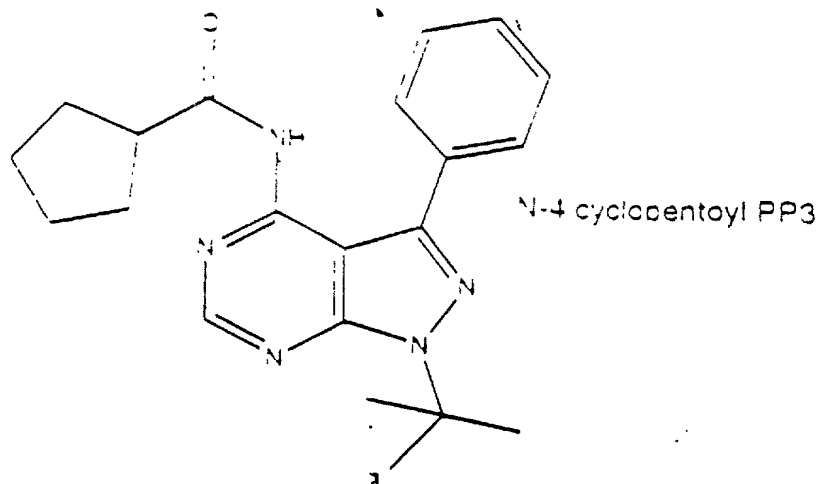


Figure 11

IC₅₀ (μM)

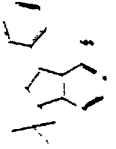
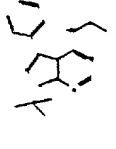
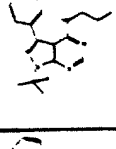
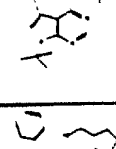
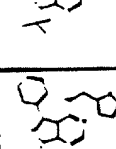
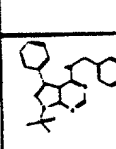
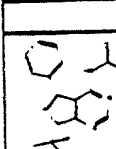
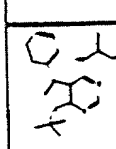

	Molecule	WT XD4	I338G XD4	WT Fyn	T339G Fyn	WT Abl	T120A Abl
a		35	0.13	0.05			<<10
b			200	>300			
c			300	>300			
d			>300	>300			
e		>300	75	>300	100		>10
f		>300	250	>300	26		>10
g		>300	85	>300	63		>10
h							
i							

Figure 12A

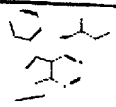
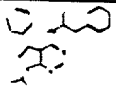
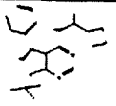
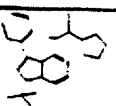
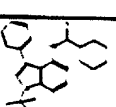
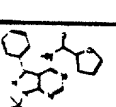
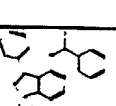
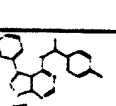
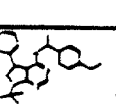
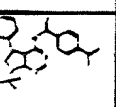
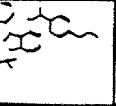
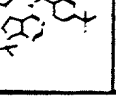
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k						
l		>300	12	6.5	5	
m		>300	19	80	9	
n		>300	20	50	5	
o		>300	150	15	19	
p		>300	10	300	11	(10
q		>300	10	300	6	(10
r			1.2			<10
s			0.63			
t			(0.411			1.8
u		>300	0.43	300	0.83	300 (10

Figure 12B

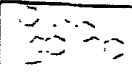
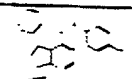
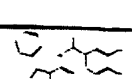
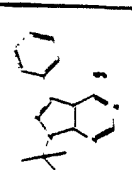
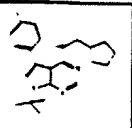
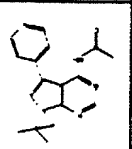
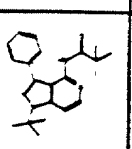
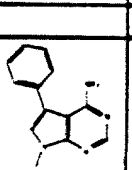
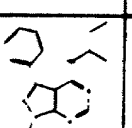
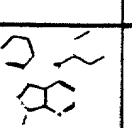
v						
w						
x						>10
y		100	(0.05	0.1		
z			>100	>300		
aa				2		
bb				7		
cc						
dd						
ee						

Figure 12C

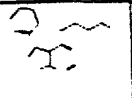
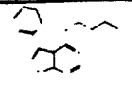
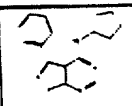
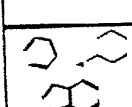
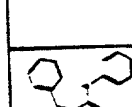
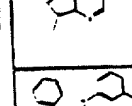
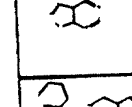
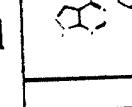
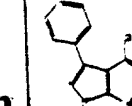
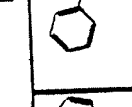
ff						
gg						
hh						
ii						
jj						
kk						
ll						
mm						
nn		>1000	0.510	0.4	<<6.5	
oo		>300	>10	>300		

Figure 12D

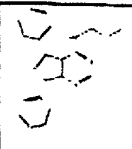
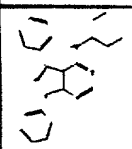
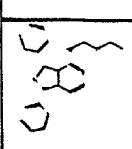
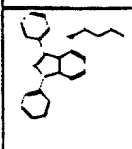
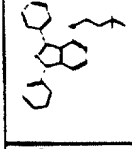
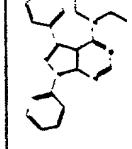
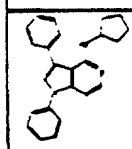
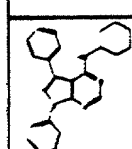
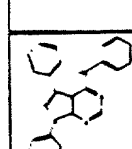
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qq		>300	>10	>300			
rr		>300	>10	>300			
ss		>300	>10	>300			
tt		>300	>10	>300			
uu		>300	>10	>300			
vv		>300	>10	>300			
ww		>300	>10	>300			
xx		>300	>10	>300			

Figure 12E

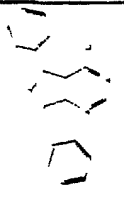
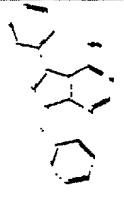
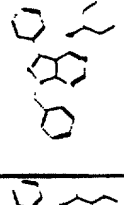
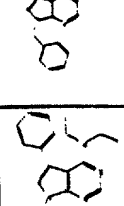
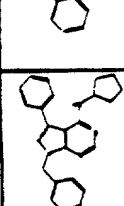
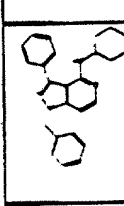
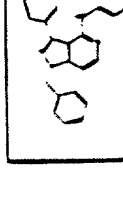

yy						
zz		<10	2.5	<<10		
aaa		>300	>10	>300		
bbb		>300	>10	>300		
ccc		>300	>10	>300		
ddd		>300	>10	>300		
eee		>300	>10	>300		
fff		>300	>10	>300		

Figure 12F

Figure 13A

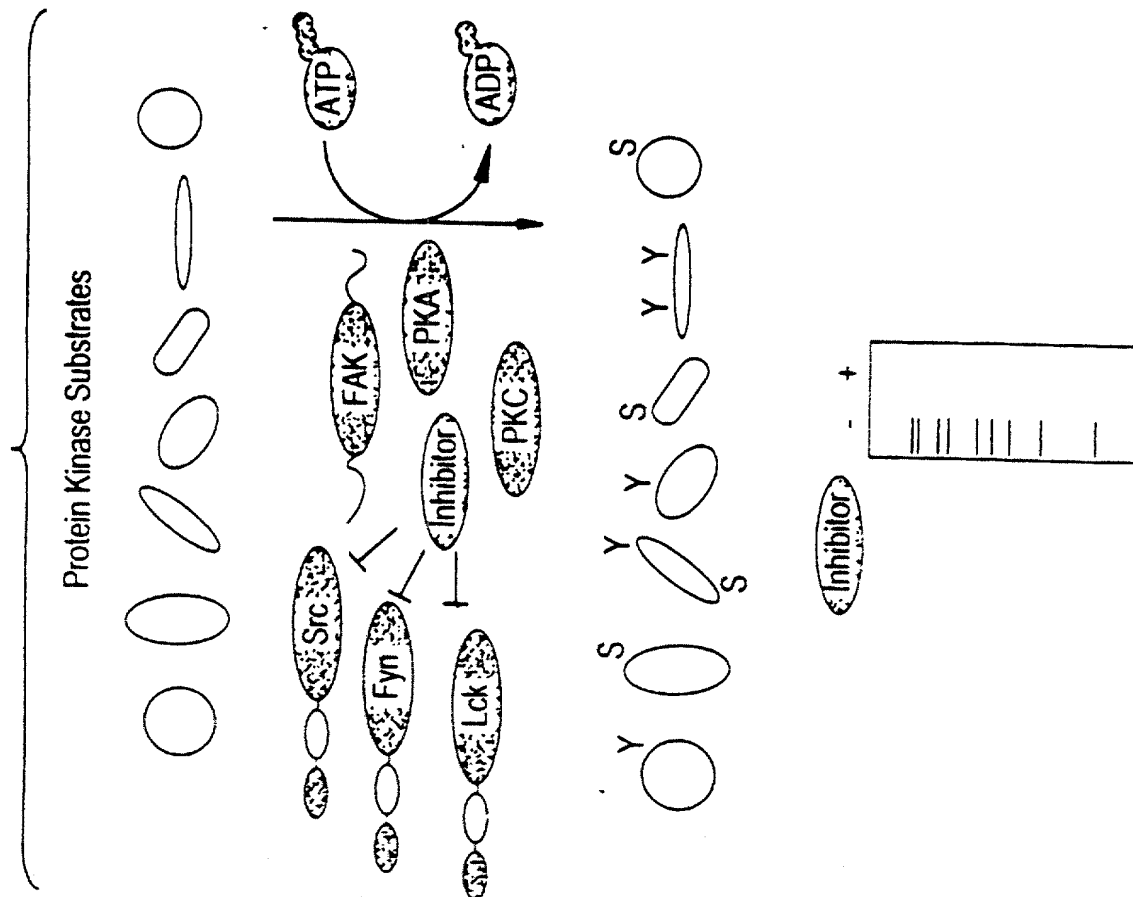
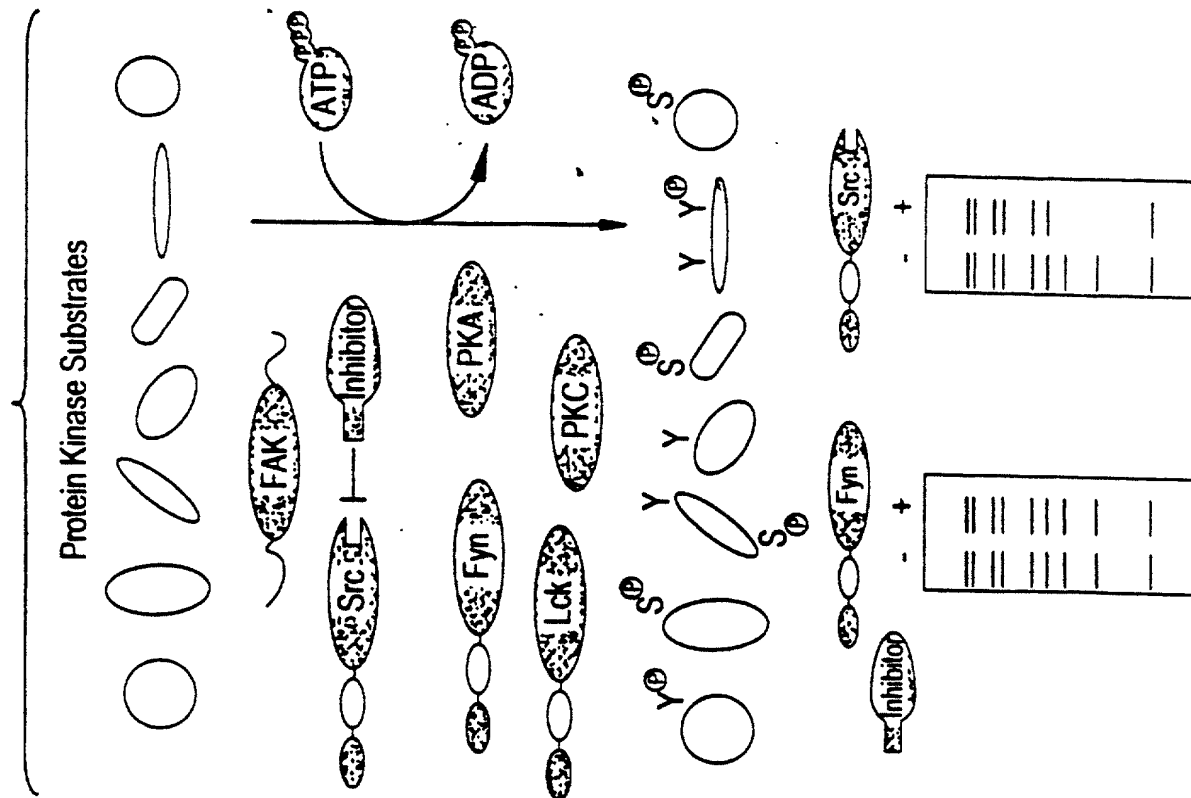


Figure 13B



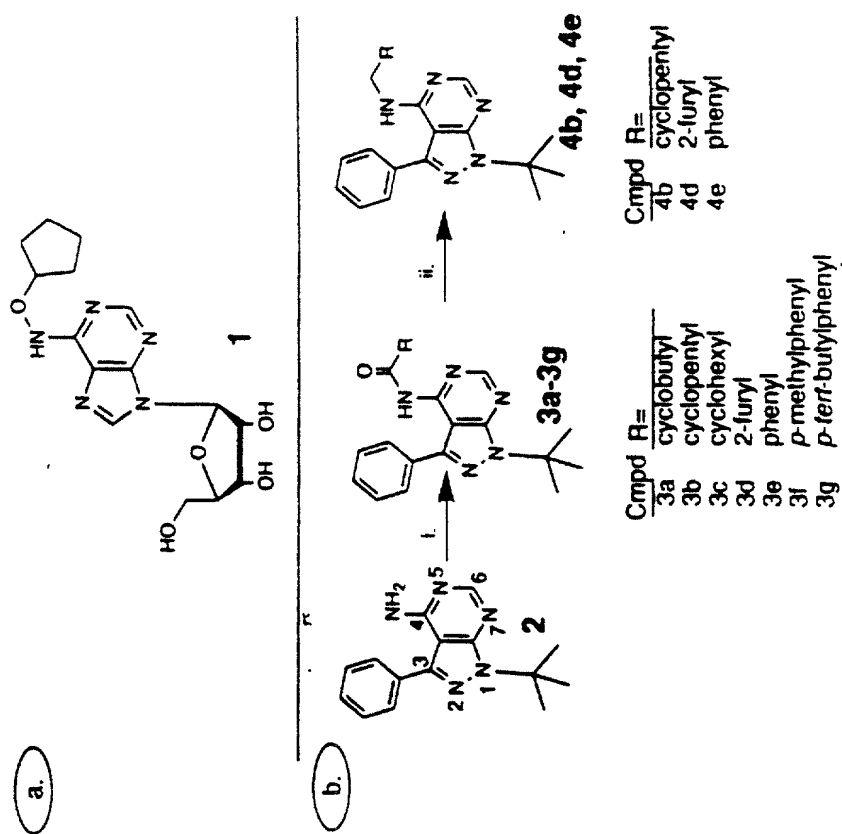


Figure 14

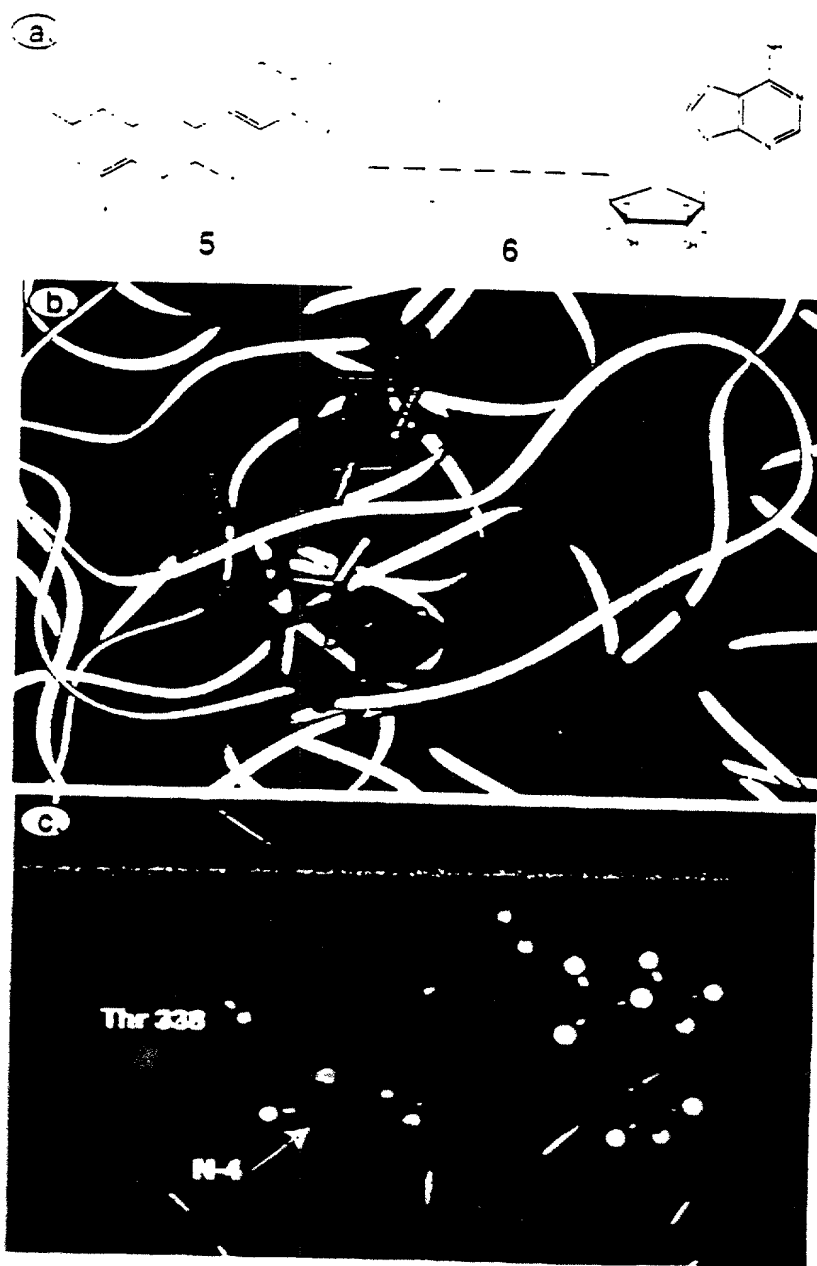


Figure 15

205170 235400

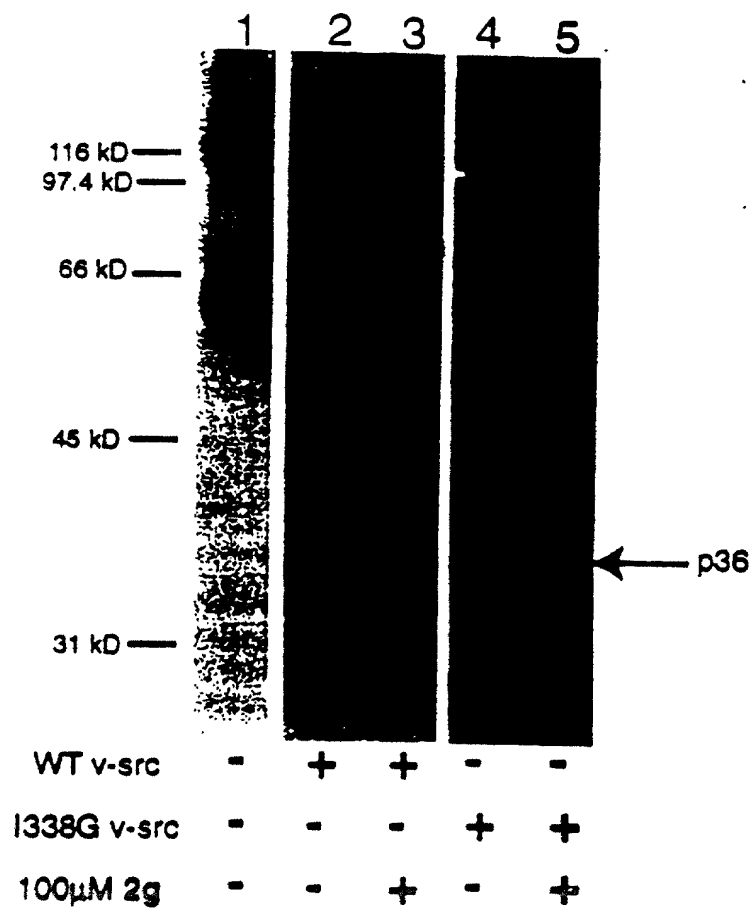


Figure 16

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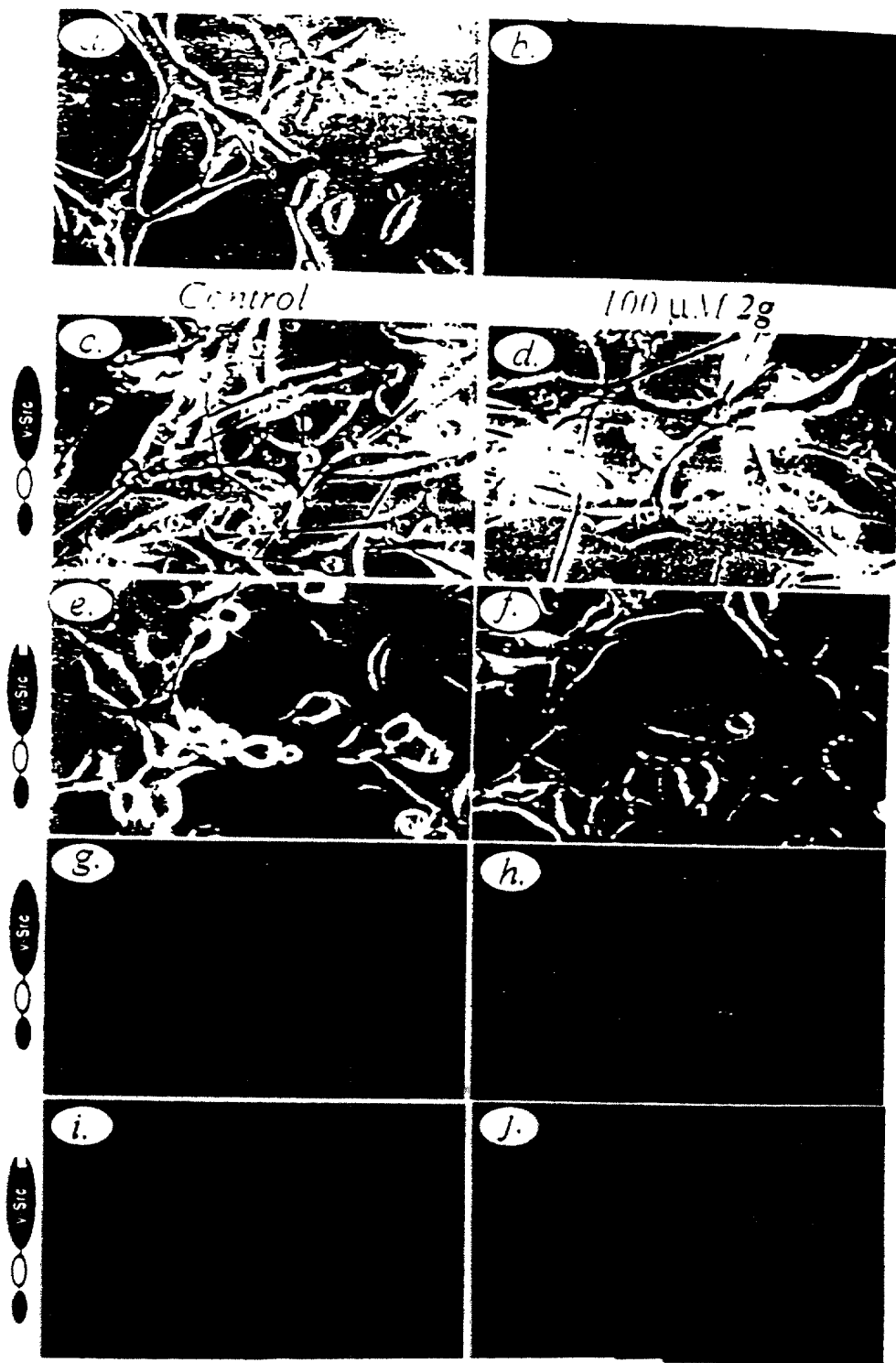
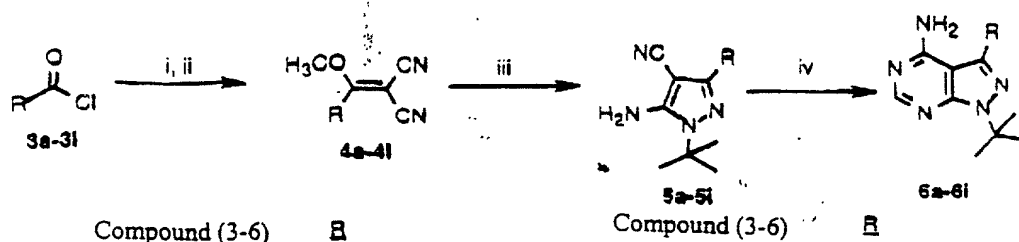
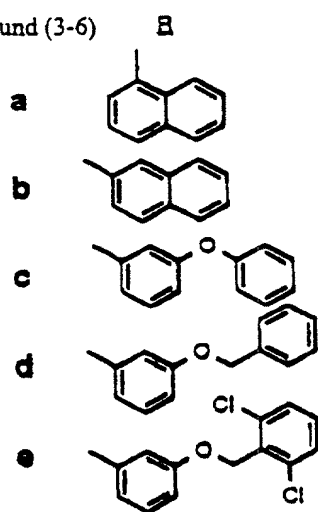


Figure 17



Compound (3-6)



Compound (3-6)

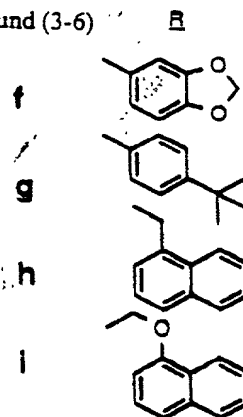


Figure 18

20040927-041002

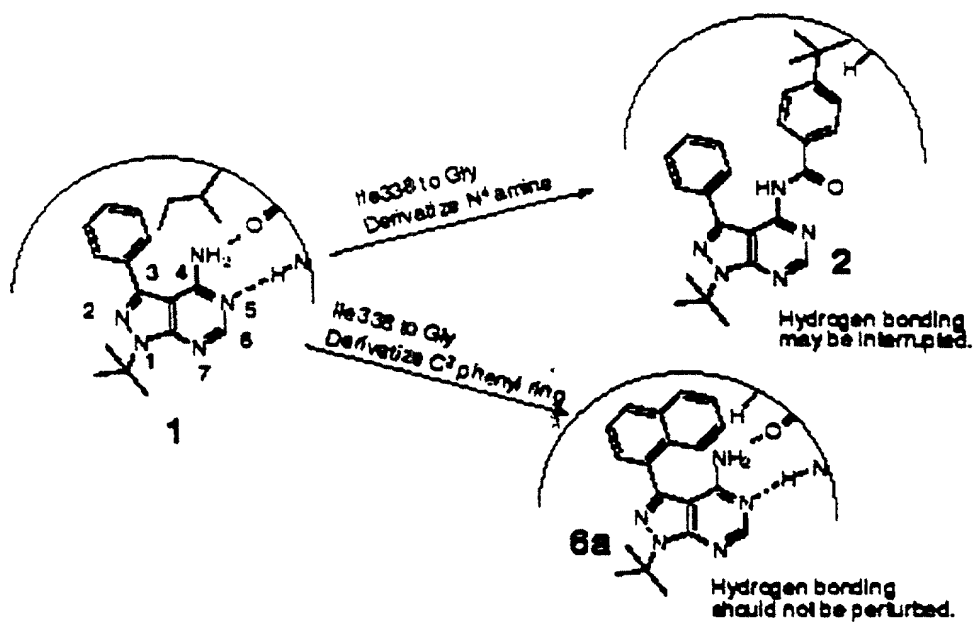


Figure 19

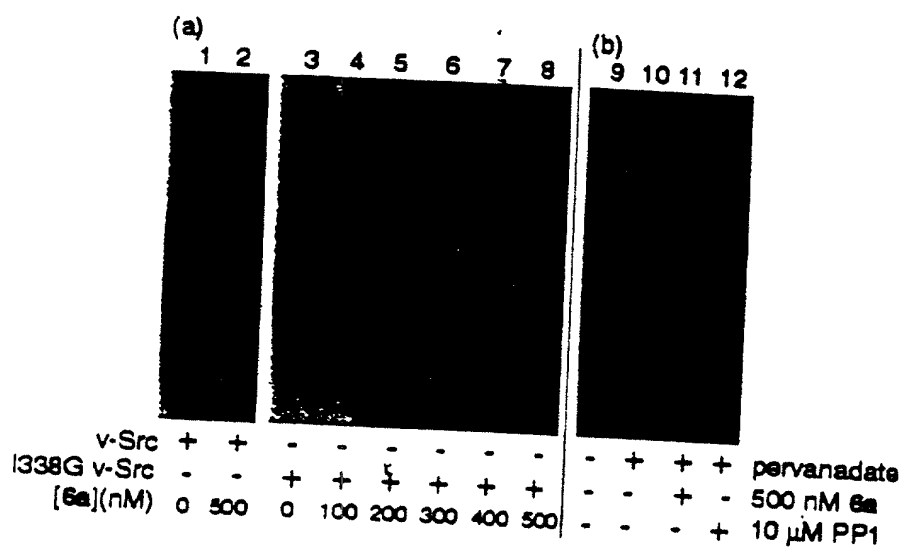


Figure 20

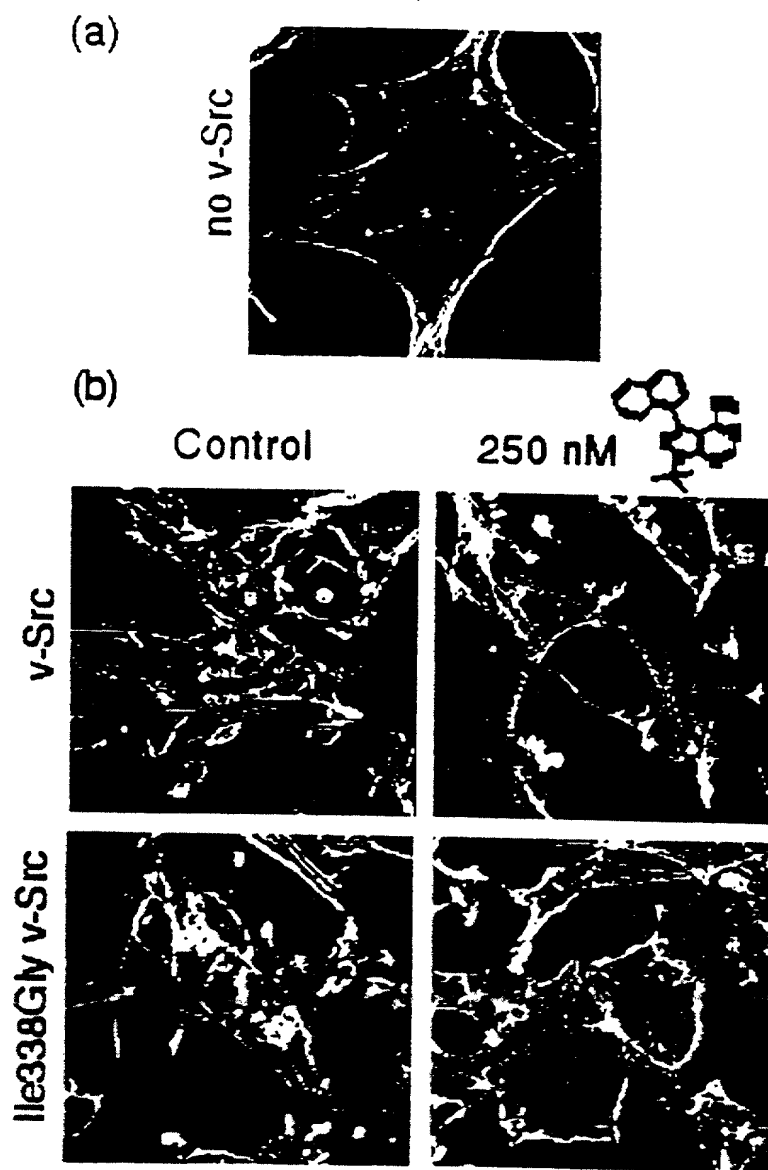


Figure 21

Figure 1

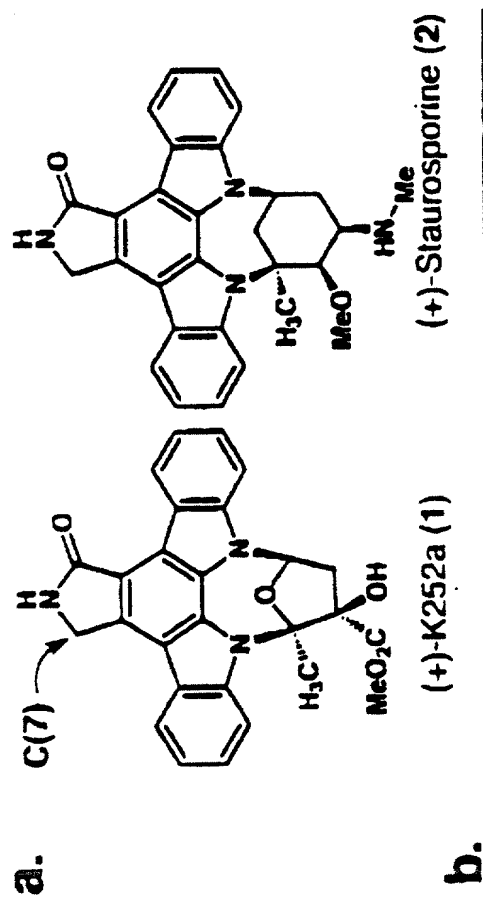


Figure 22

202510-20544001

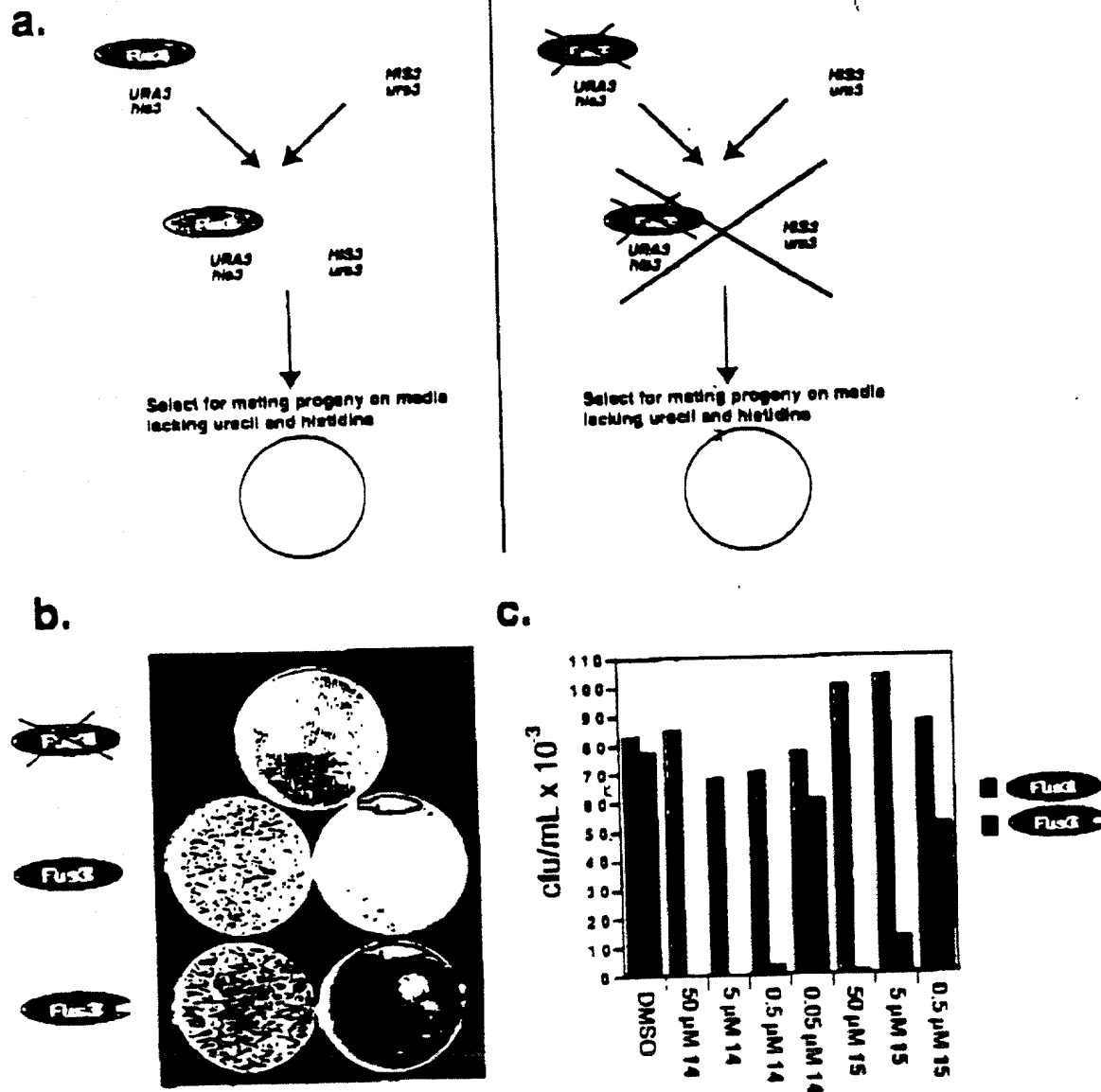
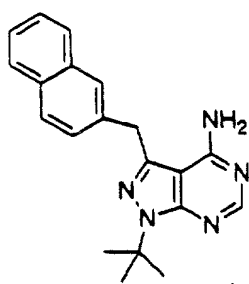


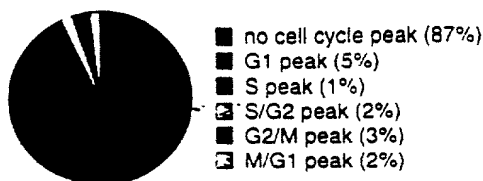
Figure 23



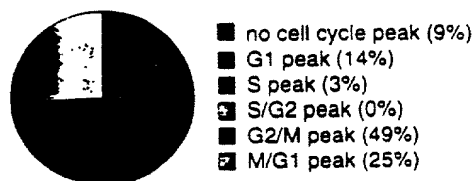
6j

Figure 24

A All *S. cerevisiae* genes (6,200)

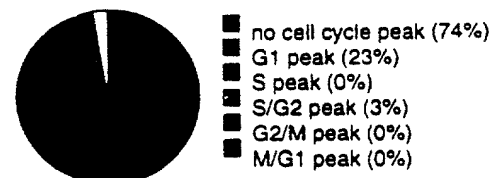


B Decreases - 120 min (66)



Unreg		S		PHO3	-21.5	M/G1	
AMH1	-3	MTB2	-4.8	PHO5	-10.8	AGA2	-6.5
BAR1	-5.1	MET14	-2.9	PRY1	-3.2	EGT2	-78.3
PUT4	-3.2			RPI1	-2.7	FAA3	-4.7
SUN4	-4.1	G2/M		SOL1	-3.8	GYP6	-2.3
YBR677C	-2.6	ALK1	-3.5	SKN1	-2.3	IAH2	-3.4
YER067W	-5.5	ATF2	-5.1	STE2	-2.5	ICS4	-4.7
		BNS1	-3.7	STE8	-5.8	NICM3	-2.5
G1		CDC20	-4.1	SUR7	-2.9	PCL3	4.9
CTS1	-28.4	CDC5	-3	SWB	-3.1	PIR1	-3.7
GPH1	-2.9	CLB2	-4.1	UTH1	-2.5	PTS1	-3.5
MFA1	-3.2	DBP2	-2.8	WSC4	-4.9	SPI1	-7.6
PRY3	-2.7	FAR1	-20.4	YDR033W	-13.8	YGP1	-5.5
RME1	-3.1	HST3	-4.1	YIL152W	-3.1	YNL045W	-5.7
RPC10	-41.2	MFA2	-6.9	YJL061W	-4	YNR067C	-19.4
SCW11	-16.4	MYO1	-3	YLR254C	-4.2	YOR065W	-3.7
YER124C	-9.8	PHO11	-4.8	YML119W	-4.1	YOR264W	-4.7
YHR218W	-3	PHO12	-5.8	YNL058C	-3.1	YPL158C	-4.6
				YRO2	-7.8		

C Increases - 120 min (38)



Unreg		G1		S/G2	
BIO3	2.6	YAR068W	4.5	CLM2	3.3
DIC1	2.6	YBR241C	3.7	CSH2	3.2
ERR1	2.8	YCR059C	2.9	PCL1	4.7
GSC2	3.2	YEL070W	3	PRY2	3
GUT2	3.9	YFL061W	3.2	SRO4	2.9
HEM13	2.8	YGL061W	2.5	YLL012W	2.8
MAL1	4.1	YGL170C	3.5	YLR328W	4
MRP20	2.7	YHR214W-A	2.8	YNL300W	2.5
NGR1	3.5	YIL169C	20.1	YPS4	3.4
PES4	3.1	YLR043C	8.1		
SKM1	2.7	YMR103C	2.7		
SPO11	5.9	YMR107W	3.5		
THI13	2.6	YOR343C	3.3		
THI21	2.5	YPL280W	3.1		

D Genomic trends

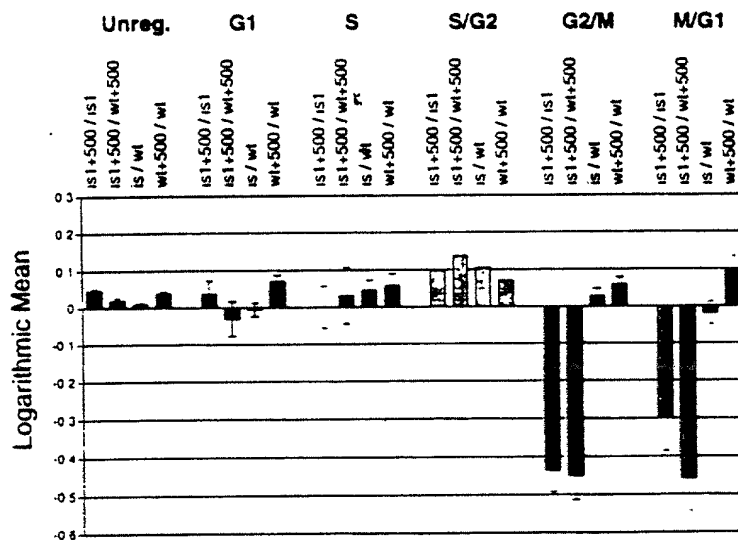


Figure 25

a.

Protein	Kinase Family	Specificity	Cellular Function
v-Src	Src	Tyr	oncogenic transformation
c-Fyn	Src	Tyr	lymphocyte activation
c-Abl	Abl	Tyr	F-actin binding, transcription
CAMK II	calcium/calmodulin dependent	Ser/Thr	long-term potentiation, memory
CDK2	cyclin dependent	Ser/Thr	mammalian cell cycle progression
CDC28	cyclin dependent	Ser/Thr	<i>S. cerevisiae</i> cell cycle progression
Fus3	mitogen-activated	Ser/Thr	<i>S. cerevisiae</i> mating

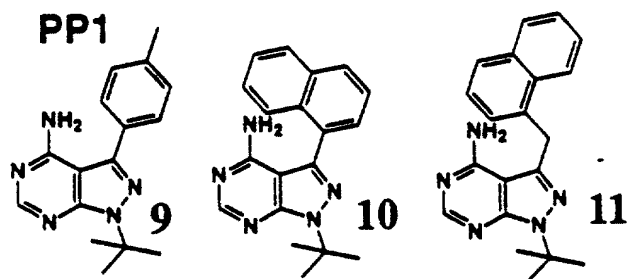
b.

v-Src	(318) RHEKLVQLYAMVSE-----EPIYIVIEYMSK--GSLLDFLKGMCKY
Fyn	(319) KHKLVQLYAVVSE-----EPIYIVTEYMNK--GSLLDFLKDGEGR
Abl	(294) KHPNLVQLLGVCCTRE-----PPFYIITEFMTY--GNLLDYLRECNRQE
CamK II	(68) KHPNIVRLHDSISEE-----GHYLI FDLVTG--GELFEDIVAREY
Cdk2	(59) NHPNIVKLLDVIHTE-----NKLYLVFEFLHQ---DLKKFMDASALTG
Cdc28	(66) KDDNIVRLYDIVHSDA-----HKLYLVFEFLDL---DLKRYMEGIPKDDP
Fus3	(67) KHENIITIFNIQRPSFENF-----NEVYIIQELMQT---DLHRVISTQM

338

**Figure 26**

Figure 27



Wild Type

v-Src	2.2	1.0	28
c-Fyn	0.050	0.60	1.0
c-Abl	0.30	0.60	3.4
CDK2	22	18	29
CAMK II	17	22	24

Engineered

v-Src	0.0015	0.0043
c-Fyn	0.0065	0.0032
c-Abl	0.0070	0.12
CDK2	0.015	0.0050
CAMK II	0.097	0.0080

Figure 28